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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/390,846	09/14/1999	JACOBUS JOHANNES KOK	I/95150-US/D	7646

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EXAMINER
SMITH, LYNETTE F

ART UNIT	PAPER NUMBER
1645	18

DATE MAILED: 06/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

Office Action Summary

Application No.	Applicant(s)
09/390,846	Kok et al
Examiner	**Art Unit**
Lynette R. F. Smith	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Dec 2, 2002*.

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-3, 11, and 13-25* is/are pending in the application.

4a) Of the above, claim(s) *14, 15, 21, 22, and 25* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-3, 11, 13, 16-20, 23, and 24* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☒ The drawing(s) filed on *Sep 14, 1999* is/are a) ☐ accepted or b) ☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☒ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. The examiner acknowledges the amendment filed 12/2/02. Claims pending are claims 1-3, 11, 13-25. Claims canceled are claims 4-10 and 12. Claims withdrawn from consideration are claims 14, 15, 21, 22 and 25. Claims under consideration are claims 1-3, 11, 13, 16-20, 23, and 24.

2. The examiner acknowledges applicant's statement concerning foreign priority. However the foreign priority document must be received in the instant application. To date the document has not been received.

3. The examiner acknowledges the statement concerning the drawings. However, corrected drawings must be received in response to this office action. The correction will not be held in abeyance.

REJECTIONS WITHDRAWN

4. In view of applicants arguments, the prior art rejections are withdrawn.

REJECTIONS MAINTAINED

5. The rejection of claims 3, 17, 18, 23 and 24 under 35 U.S.C. 112 first paragraph is maintained for reasons set forth in the previous office action.

The rejection was on the grounds that the specification, while being enabling for an isolated 37kd protein from Eimeria acervulina consisting of the amino acid sequence set forth in seq. I.D. No. 2 and a vaccine comprising the 37kd protein, does not reasonably provide enablement for any fragment of the isolated protein. The specification does not enable any

person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are broadly drawn to an isolated protein, fragments, biological variants and equivalents of the protein for use in a vaccine composition. The specification does not enable all variants and equivalents of the claimed protein. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of proteins broadly encompassed by the claims and the claims broadly encompass a significant number of inoperative species. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, the problem of predicting protein structure from mere sequence data of a single protein and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein and finally what changes can be tolerated with respect thereto is extremely complex and well outside the realm of routine experimentation.

While recombinant and mutagenesis techniques are known, it is **not** routine in the art to screen for multiple substitutions or multiple modifications of other types and the positions within the protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining similar activity are limited in any protein and the result of such modifications is unpredictable based on the instant disclosure. One skilled in the art would expect any tolerance to modification shown for a given protein to diminish with each further and additional modification, e.g. multiple substitutions. The sequence of some proteins is highly conserved and one skilled in the art would not expect tolerance to any amino acids modification in such proteins.

The specification does not support the broad scope of the claims which encompass all modifications and fragments because the specification does **not** disclose the following :

- the general tolerance to modification and extent of such tolerance;

- specific positions and regions of the sequence(s) which can be predictably modified and which regions are critical;

- what fragments, if any, can be made which retain the biological activity of the intact protein; and

- the specification provide essentially no guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have **not** provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed protein in manner reasonably correlated with the scope of the claims broadly including any number of additions, deletions or substitutions and fragments of any size. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, the changes which can be made in the proteins structure and still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See Amgen, Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991) at 18 USPQ2d 1026-1027 and Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. & Int. 1986). In view of all of the above it is determine that it would require undue experimentation of one of skill in the art to make and use the invention commensurate in scope with the claimed subject matter.

Applicant urges that what is claimed is one or more immunoreactive fragments which is defined by the specification, one can routinely determine fragments of a protein, biological equivalents are defined in the specification and methods for establishing LDH activity of Eimeria protein are well known in the art and cites case law in support.

It is the examiner's position that page 6, lines 12-15 do not disclose any amino acid sequence of LDH which is defined as being "immunoreactive and/or antigenic determinants", "a biologically active variant" or "an immunologically active part". What is the amino acid structure of the subsequence which meets the definition of "immunogenic determinant" or fragment of the LDH protein? The claims are not drawn to a method of measuring LDH activity. The claims are drawn to vaccines and immunoreactive fragments of the protein. The specification describes one peptide fragment, GWIKQEEVDDIVQK, which is found in seq. I.D. No.2. The specification, however, appears to lack enablement for the use of this fragment in a vaccine to protect (i.e. immunizing activity) against infection and disease caused by Eimeria. It appears that applicant is

inviting one to experiment to determine how to use the peptide fragment to protect against disease and additionally to determine what other fragments can be generated from LDH with the claimed immunoreactivity. This experimentation is considered undue and the rejection is therefore maintained.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-3, 11, 13, 16-20, 23 and 24 are rejected under 35 U.S.C. 102(b) as being anticipated by Shirley, 1975, Parasitology, 71:369-376.

The claims are drawn to an isolated protein comprising one or more immunoreactive determinants of lactate dehydrogenase enzyme from Eimeria acervulina, immunogenic fragments and vaccines comprising the protein and immunogenic fragments in pharmaceutical carriers as well as a process for preparing a vaccine.

Shirley teaches lactate dehydrogenase enzyme from *E. acervulina*. The enzyme was prepared in NaCl solution (pharmaceutical carrier) and purified from sporozoites, oocysts and

merozoites (pages 372, 373 and plate 1A). The protein of Shirley appears to be the same as the claimed protein. The formulation of the enzyme in NaCl meets the limitations of the claimed process. Characteristics such as immunoreactive determinants and amino acid seq. I.D. No. 2 would be inherent in the enzyme of the prior art. The recitation of "vaccine" is being viewed as intended use of the enzyme. Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Additionally, since the Office does not have the facilities for examining and comparing applicants' protein, vaccine and process with the protein, vaccine and process of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product, vaccine and process and the product, vaccine and process of the prior art (i.e., that the protein, vaccine and process of the prior art does not possess the same material structural and functional characteristics of the claimed protein, vaccine and process). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

7. Claims 1-3, 16-18 and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Kucera, 1989, Folia Parasitologica 36(4):295-299.

The claims are drawn to an isolated protein comprising one or more immunoreactive determinants of lactate dehydrogenase enzyme from Eimeria acervulina, immunogenic fragments and vaccines comprising the protein and immunogenic fragments in pharmaceutical carriers.

Kucera teaches the lactate dehydrogenase enzyme from Eimeria acervulina and the isolation and purification of the enzyme (page 296, figure 3). The protein of Kucera appears to be the same as the claimed protein. Characteristics such as immunoreactive determinants and amino acid seq. I.D. No. 2 would be inherent in the enzyme of the prior art. The recitation of "vaccine" is being viewed as intended use of the enzyme. Applicant's use of the open-ended term "comprising" in the claims fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Additionally, since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

8. Claims 1-3, 16-18, and 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Nakamura et al, 1991, Journal of Veterinary Medical Science, 53(6):1101-1103.

The claims are drawn to an isolated protein comprising one or more immunoreactive determinants of lactate dehydrogenase enzyme from Eimeria acervulina, immunogenic fragments and vaccines comprising the protein and immunogenic fragments in pharmaceutical carriers.

Nakamura et al teach the lactate dehydrogenase enzyme from Eimeria acervulina and the isolation and purification of the enzyme (figure 2, c,d,f). The protein of Nakamura et al appears to be the same as the claimed protein. Characteristics such as immunoreactive determinants and amino acid seq. I.D. No. 2 would be inherent in the enzyme of the prior art. The recitation of "vaccine" is being viewed as intended use of the enzyme. Applicant's use of the open-ended term "comprises" in the claims fails to exclude unrecited steps and leaves the claims open for inclusion of unspecified ingredients, even in major amounts. See In re Horvitz, 168 F 2d 522, 78 U.S.P.Q. 79 (C.C.P.A. 1948) and Ex parte Davis et al., 80 U.S.P.Q. 448 (PTO d. App. 1948). Additionally, since the Office does not have the facilities for examining and comparing applicants' protein with the protein of the prior art, the burden is on applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e., that the protein of the prior art does not possess the same material structural and functional characteristics of the claimed protein). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

9. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Shirley, 1979, Parasitology 78:221-237, teaches the lactate dehydrogenase enzyme from Eimeria acervulina and cross-immunity tests.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SPE Lynette R. F. Smith whose telephone number is 703-308-3909. The examiner can normally be reached on weekdays from 8:30 am to 6:00 pm and alternate Fridays.

The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Smith/lfs

L.F. Smith

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